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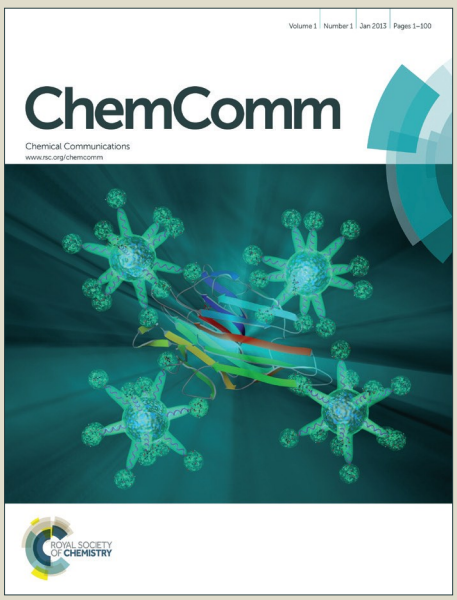

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Iodine-promoted cyclization of *N*-propynyl amides and *N*-allyl amides via sulfonylation and sulfenylation

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An iodine-promoted regioselective cyclization of *N*-propynyl/allyl amides with sulfonyl hydrazides has been developed for the synthesis of 5-methyl-arylsulfonyloxazoles and 5-methyl-arylthiooxazolines via sulfonylation and sulfenylation reactions. The notable features of this reaction are the formation of new C-S and C-O bonds, the broad functional group tolerance, and its applicability to alkyl sulfonyl hydrazides as well as internal alkynes.

Sulfones and thioethers are important classes of functional groups with diverse applications as bioactive substituents.[1] Likewise, oxazoles and oxazolines are pivotal classes of oxaza heterocycles because of their widespread use in chemistry and biological applications.[2] Therefore, sulfur-containing oxaza heterocyles are of potential biological interest (Figure 1).[3]

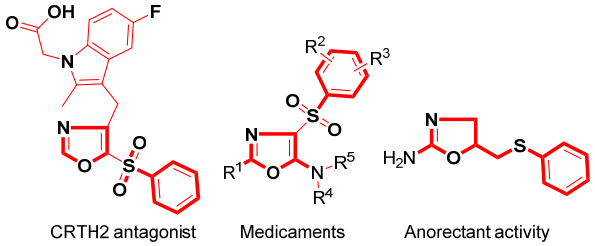
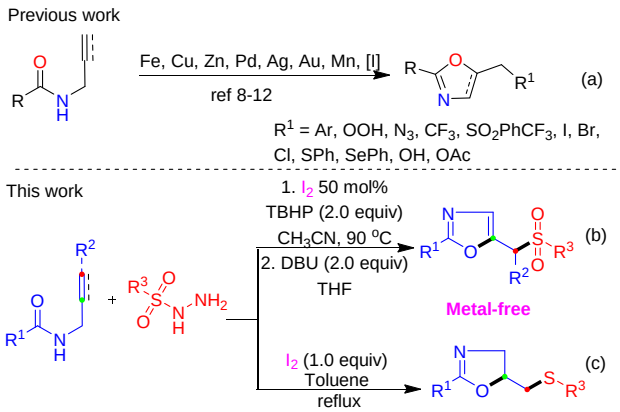


Figure 1. Bioactive sulfur-containing oxazole and oxazoline heterocycles.

In the last decade, *N*-propargyl amides have gained significant popularity in the synthesis of oxazoles and oxazolines;[4,5] however, difficulties in controlling exo vs endo selectivity[6] and low feasibility with internal alkynes[7] are major drawbacks. Recently, an alternative strategy was used to overcome this issue by in situ installation of functional groups such as aryl,[8] peroxy,[9] azide,[10] trifluoromethyl,[10] sulfonyl[10] and allylic alkylation[11] at the endo carbon of *N*-propargylamides under transition-metal catalysis (Scheme 1a). Similarly, the synthesis of oxazolines from *N*-allylamides has been achieved with the insertion of a variety of functional groups[12] under metal-catalysed as well as metal-free conditions (Scheme 1a).

Recently, sulfonyl hydrazides have been used to install sulfonyl or thioether functional groups in organic molecules, depending on reaction conditions.[13,14] As part of our ongoing research in metal-free reactions and oxaza heterocycle synthesis,[15,5a] we wish to extend the utilization of sulfonyl hydrazides to generate β-iodovinylsulfones from *N*-propargyl amides with I_2/TBHP, followed by intramolecular cyclization in the presence of 1,8-Diazabicycloundec-7-ene (DBU) in a sequential one-pot method (Scheme 1b), for the synthesis of 2,5-disubstituted oxazoles. In addition, we disclose the synthesis of oxazolines from *N*-allylamides through electrophilic addition to an in situ generated sulfenyl iodide (Scheme 1c).



Scheme 1. Previous studies and this work towards the in situ functionalization of *N*-propynyl or *N*-allyl amide

Our preliminary investigation began with propargyl amide **1a** and tosyl hydrazide **2a** as model substrates, as shown in Table 1. To our surprise, *N*-((*E*)-2-iodo-3-tosyl-allyl)benzamide **3aa** was obtained in 67% when these substrates were treated

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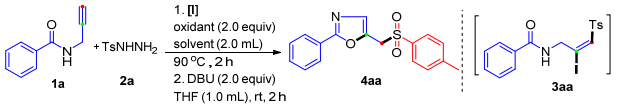
Table 1. Optimization of the reaction conditions[a]



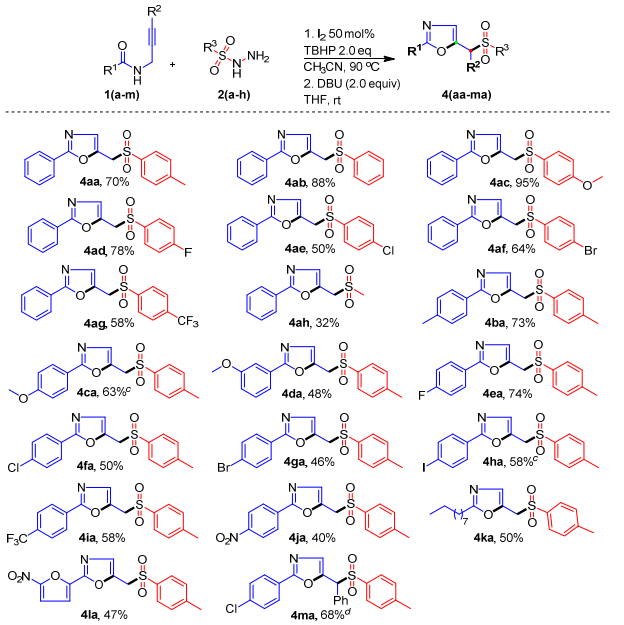
entry	I source (x equiv)	oxidant (y equiv)	solvent	yield (%)	
				3aa[b]	4aa[c]
1	NIS (50)	TBHP (2)	CH_3CN	67	62
2	TBAI (50)	TBHP (2)	CH_3CN	25	20
3	KI (50)	TBHP (2)	CH_3CN	26	21
4	I_2 (50)	TBHP (2)	CH_3CN	75	70
5	I_2 (25)	TBHP (2)	CH_3CN	50	45
6	I_2 (50)	TBHP (1.5)	CH_3CN	60	54
7[d]	I_2 (50)	TBHP (2)	CH_3CN	65	60
8	I_2 (50)	CHP (2)	CH_3CN	64	59
9[e]	I_2 (50)	TBHP(2)	CH_3CN	40	35
10	I_2 (50)	DTBP (2)	CH_3CN	<10	-
11[f]	I_2 (50)	H_2O_2 (2)	CH_3CN	<10	-
12	I_2 (50)	$K_2S_2O_8$ (2)	CH_3CN	<10	-
13	I_2 (50)	TBHP (2)	1,4-dioxane	15	-
14	I_2 (50)	TBHP (2)	THF	<5	-
15	I_2 (50)	TBHP (2)	DMSO	0	-
16	I_2 (50)	TBHP (2)	DMF	0	-
17	I_2 (50)	TBHP (2)	toluene	<10	-
18[g]	I_2 (50)	TBHP (2)	CH_3CN	75	21
19[h]	I_2 (50)	TBHP (2)	CH_3CN	75	30
20[i]	I_2 (50)	TBHP (2)	CH_3CN	75	45
21[j]	I_2 (50)	TBHP (2)	CH_3CN	75	63
22[k]	I_2 (50)	TBHP (2)	CH_3CN	75	64
23		TBHP (2)	CH_3CN	-	-

[a] Reaction condition: **1a** (1.0 mmol), **2a** (2.0 mmol), iodine source (x equiv), oxidant (y equiv), solvent (2.0 mL) and stirred for 2 h at 90 °C, then cooled to rt and diluted with THF (1.0 mL) followed by addition of DBU (2.0 equiv) and stirred at rt for another 2h unless otherwise noted. [b] Determined by GC-mass analysis. [c] Isolated yields. [d] 1.5 mmol of **2a** was used [e] TBHP (5-6 M in decane). [f] 30% H_2O_2. [g] DABCO (2.0 equiv). [h] K_2CO_3 (2.0 equiv). [i] Cs_2CO_3 (2.0 equiv). [j] 1.0 equiv DBU was used. [k] DBU (2.0 equiv) was added without THF.

with NIS (50 mol %) and TBHP (2.0 equiv) in acetonitrile for 2 h at 90 °C. The resultant compound was further treated with 2.0 equiv of DBU and THF (1.0 mL) to yield 2-phenyl-5-(tosylmethyl)oxazole **4aa** in 62% yield in a sequential one-pot reaction (Table 1, entry 1). The structure of compound **4aa** was confirmed using X-ray analysis.[16] Subsequent work (Table 1, entries 2-4) revealed that 50 mol% I_2 followed by treatment with DBU gave **4aa** at a 70% yield. Lowering the quantities of I_2, TBHP, and tosyl hydrazide, or screening other oxidants such as CHP, TBHP (5-6 M decane), DTBP, 30% H_2O_2, and $K_2S_2O_8$, resulted in lower yields (Table 1, entries 5-12). The effect of solvents was tested using dioxane, THF, DMSO, DMF, and toluene (Table 1, entries 13-17). However, no solvents resulted in improved yields. Bases besides DBU, such as DABCO, K_2CO_3 and Cs_2CO_3, led to lower conversion (Table 1, entries 18-20). The yield of **4aa** was reduced when only 1.0 equiv of DBU was used or when THF was omitted (Table 1, entries 21-22). The reaction gave a complex mixture in the absence of iodine (Table 1, entry 23). Thus, of the reaction conditions screened in Table 1, entry 4 was chosen as the optimum conditions.

The scope of this methodology was investigated by screening *N*-propynylamides **1**(**a**-**m**) and aryl sulfonyl hydrazides **2**(**a**-**h**) under the standard conditions, as shown in Table 2. The reaction worked well with benzene sulfonyl hydrazide (**2b**) as well as with a series of substituents of aryl functionalities such as *p*-MeO (**2c**), *p*-F (**2d**), *p*-Cl (**2e**), *p*-Br (**2f**), and *p*-CF_3 (**2g**) to afford oxazole derivatives **4**(**ab**-**ag**) in 50-95% yield. Surprisingly, the reaction worked with mesyl hydrazide (**2h**) to produce the corresponding alkyl derivative **4ah**, albeit in low yield. Substituted phenyl groups were tested at R^1, including electron-donating groups such as *p*-Me (**1b**), *p*-MeO (**1c**) and *m*-MeO (**1d**), as well as electron-withdrawing groups such as *p*-F (**1e**), *p*-Cl (**1f**), *p*-Br (**1g**), *p*-I (**1h**), *p*-CF_3 (**1i**) and *p*-NO_2 (**1j**). The reaction proceeded well to give compounds **4**(**ba**-**ja**) at 40-74% yields. Cumene hydroperoxide (CHP) was required for *p*-MeO (**1c**) and *p*-I (**1h**) due to low yields with TBHP. The reaction underwent smooth conversion when the aryl group was replaced with alkyl (**1k**) and heteroaryl (**1m**) groups to generate **4**(**ka**-**la**) in moderate yields. Finally, the reaction also worked well with internal alkyne **1m** to produce **4ma** at a 68% yield. The structures of compounds **4ab**, **4ac**, **4ad**, **4af**, **4ag** and **4ma** were confirmed by X-ray analysis.[16]

Table 2. Scope of *N*-propynylamides and sulfonyl hydrazides[a,b]



[a] Reaction conditions: compound **1a**-**m** (1.0 mmol), sulfonyl hydrazide **2a**-**h** (2.0 mmol), I_2 (50 mol%), TBHP (2.0 equiv), CH_3CN (2.0 mL), 90 °C, 2-5 h, then DBU (2.0 equiv), THF (1.0 mL), rt, 2-5 h. [b] isolated yields. [c] CHP was used instead of TBHP. [c] Without the addition of DBU the intermediate **3ja'** was isolated at a 45% yield; the structure was confirmed by X-ray. [d] After adding DBU (2.0 equiv) reaction was stirred for 24 h at 80 °C.

The synthetic feasibility of this procedure was extended to the reaction of α,α'-disubstituted propynyl amides **1**(**n**-**o**) with tosyl hydrazide (**2a**) for the synthesis of vinyl sulfones as shown in Scheme 2 (eqs. 1 and 2). The reaction went smoothly to produce vinyl sulfones **4na**-**oa** in 50-53% yields. The structure of **4oa** was confirmed by X-ray analysis.[16]

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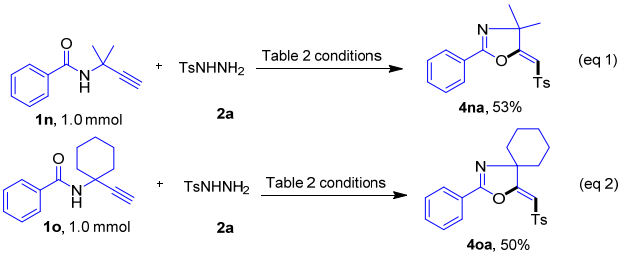
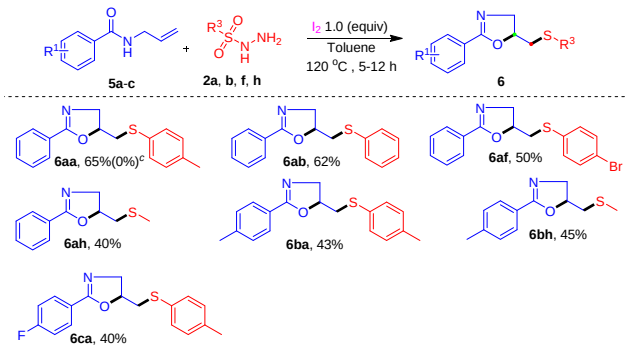


Scheme 2. Synthesis of vinyl sulfones.

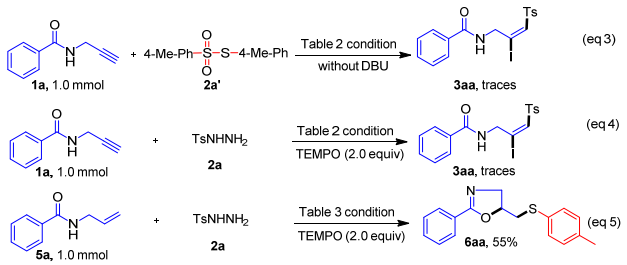
Following the successful synthesis of the oxazole derivatives, we investigated the scope of the reaction between *N*-allyl benzamide (**5a**) and tosyl hydrazide (**2a**) using the standard conditions. However, the desired oxazoline was not obtained; instead, *N*-(2-hydroxy-3-tosylpropyl)benzamide **6aa'** was isolated at low yields.[17] Interestingly, 5-((*p*-tolylthio)methyl)-4,5-dihydro-2-phenyloxazole **6aa** was isolated at 65% yields when the conditions were changed to I_2 (1.0 equiv) in toluene at 120 °C for 5 h (Table 3).[18] Next, the scope the reaction between allyl amides and aryl hydrazides was evaluated using benzene sulfonyl hydrazide (**2b**) and 4-bromo benzene sulfonyl hydrazide (**2f**). The reaction was successful in both the cases, affording oxazoline derivatives **6ab** and **6af** at 62% and 50% yields, respectively. The reaction also worked for mesyl hydrazide (**2h**) to give corresponding alkylthioethers **6ah** and **6bh** in moderate yields. Finally, the reaction also proceeded with the R^1 substituted aryls *p*-Me (**5b**) and *p*-F (**5c**), to produce **6**(**ba**-**ca**) at 40-43% yields.

Table 3. Scope of *N*-allylamides and sulfonyl hydrazides[a,b]



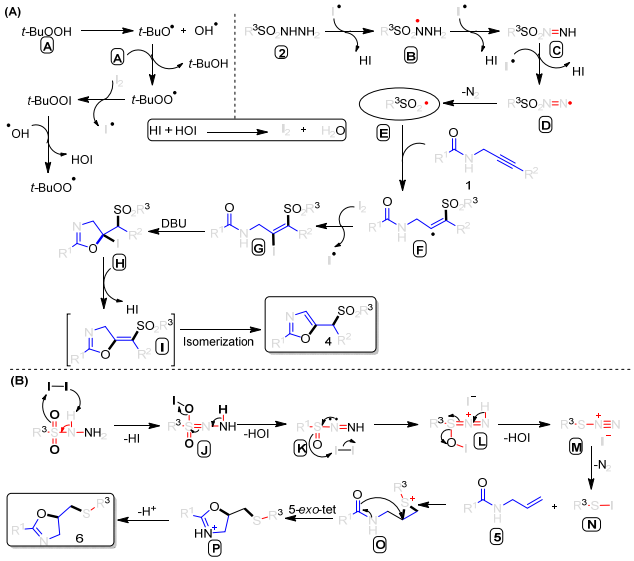
[a] Reaction conditions: compounds **5a**-**c** (1.0 mmol), sulfonyl hydrazide **2a**, **b**, **f**, **h** (1.5 mmol), I_2 (1.0 equiv), toluene (2.0 mL) at 120 °C for 5-7 h. [b] isolated yields. [c] In the absence of iodine, *S*-(*p*-tolyl) 4-methylbenzenesulfonothioate was isolated as major product and 1,2-di-*p*-tolyldisulfane was isolated as minor product with recovery of **5a**.

To understand the reaction mechanism, the control experiments shown in Scheme 3 were carried out. The reaction of *N*-propargyl amide **1a** with *S*-*p*-tolyl-4-methyl benzene sulfonothioate **2a'** under the standard condition without DBU gave trace amounts of *N*-((*E*)-2-iodo-3-tosylallyl)benzamide **3aa** (Scheme 3, eq. 3). This result suggests that **2a'** is not a key intermediate formed in the reaction.[19a] Next, the reaction of **1a** and **2a** under standard conditions from Table 2 in the presence of TEMPO gave trace or no product (Scheme 3, eq. 4). Finally, the reaction of **5a** and **2a** under the standard conditions from Table 3 with TEMPO gave the compound 5aa at a 55% yield (Scheme 3, eq. 5). These results suggest that the sulfonylation reaction proceeds via radical reaction and that the sulfenylation proceeds through a non-radical pathway.



Scheme 3. Control studies.

A plausible mechanism for the formation of oxazoles and oxazolines based on control studies and previously reported literatures[13,14e,f] is shown in Scheme 4. The reaction is proposed to involve a sulfonyl radical **E**, which is generated by the reaction of I_2 with TBHP through the elimination of N_2. The attack of the resulting sulfonyl radical **E** to *N*-propynylamide **1** gives the vinyl radical **F**. The vinyl radical is trapped by I_2 to afford β-iodovinylsulfone **G**.[13e] Then, the reaction of the β-iodovinylsulfone with DBU gives the 5-exo-trig product **H**. The elimination of HI from intermediate **H** followed by the isomerization gave the oxazole derivative **4**[19b] (Scheme 4A).



Scheme 4. Proposed mechanism for oxazoles and oxazolines.

On the other hand, upon reaction with iodine, sulfonyl hydrazide **2** undergoes sequential eliminations of HI and HOI to form sulfenyl iodide **N** via arylthiodiazonium salt **M**.[14e,f] The electrophilic addition of sulfenyl iodide **N** to *N*-allylamide **5** gives the sulfonium intermediate **O**. The 5-exo-tet-cyclization of intermediate **O** gives the intermediate **P**, which is deprotonated to give the oxazoline derivative **6**.

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In conclusion, we have developed a metal-free approach for the synthesis of 5-methyl-arylsulfonyloxazoles by iodine-promoted sulfonylation of *N*-propynyl amides with sulfonyl hydrazides followed by DBU-mediated cyclization. Similarly, the oxysulfenylation of *N*-allyl amides, which proceeded via the electrophilic addition of in situ generated sulfenyl iodide, produced 5-methyl-arylthiooxazolines. The key features of these reactions are broad functional group tolerance, mild conditions, the formation of two new bonds (C-S and C-O) and applicability to alkyl sulfonyl hydrazides as well as to internal alkynes.

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16 The CCDC number for the compounds **4aa** (1465160), **4ab** (1465161), **4ac** (1465166), **4ad** (1465163), **4af** (1465164), **4ag** (1465165), **4ma** (1465167), **4oa** (1465162), and **3ja'** (1473425).

17 When *N*-allylbenzamide **5a** and tosylhydrazides **2a** was treated with I_2/TBHP, the desired oxazoline was not isolated instead *N*-(2-hydroxy-3-tosylpropyl)benzamide **6aa'** was isolated in less than 10% along with other unidentified compounds.

18 For complete optimization of reaction condition (see the ESI†).

19 (a) The sulfonyl radical does not form via the intermediate *S*-*p*-tolyl-4-methylbenzenesulfonothioate **2a'** as proposed in ref 13c; (b) Intermediate **H** was proposed based on the acidity of the methylene proton and result obtained from Scheme 2.